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| 10/076,840 | 02/15/2002 | Andrew J. Murphy | REG 780D | 2776 |

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| EXAMINER | |
|---|---|
| TON, THAIAN N | |
| **ART UNIT** | **PAPER NUMBER** |
| 1632 | |

DATE MAILED: 04/06/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/076,840 | MURPHY ET AL. | |
| | Examiner | Art Unit | |
| | Thaian N. Ton | 1632 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *10 January 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *51-58,60,63-71,75 and 76* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *51-58,60,63-71,75 and 76* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## DETAILED ACTION

Applicants' Amendment, filed 1/10/05, has been entered. Claims 59, 61-62, 72-74 and 77-78 have been cancelled. Claims 51-58, 60, 63-71 and 75-76 are pending and under current examination.

### *Specification*

The objection to the disclosure for containing an embedded hyperlink and/or other form of browser-executable code is withdrawn in view of Applicants' amendment to the specification.

### *Claim Objections*

The prior objections of claims 62, 74 and 78 are rendered moot in view of the cancellation of the claims.

The prior objection of claim76 is maintained for reasons of record. The claim recites the method of claim 74. Claim 74 has been cancelled. Appropriate correction is required.

### *Double Patenting*

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214

USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 51-58, 60, 63-71 and 75-76 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-14 of U.S. Patent No. 6,586,251 B2.

Claims 51-58, 60, 63-71 and 75-76 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-17 of U.S. Patent No. 6,596,541 B2.

Applicants state that they will submit a terminal disclaimer upon indication of allowable claims. See p. 7, part II of the Response. As no terminal disclaimer(s) has been filed, these rejections are maintained for reasons of record.

### *Claim Rejections - 35 USC § 112*

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 51-58, 60, 63-71 and 75-76 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for mouse embryonic stem [ES] cells comprising a modified endogenous gene locus flanked by site-specific recombination sites, the specification does not reasonably provide enablement for ES cells comprising a modified endogenous gene locus flanked by site-specific recombination sites, for the breadth claimed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or us the invention commensurate in scope with these claims. The rejection is maintained for reasons of record.

Enablement is considered in view of the Wands factors (MPEP 2164.01(A)). These include: nature of the invention, breadth of the claims, guidance of the specification, the existence of working examples, state of the art, predictability of the art and the amount of experimentation necessary. All of the Wands factors have been considered with regard to the instant claims, with the most relevant factors discussed below.

Applicants traverse the rejection on ground that one of skill in the art would readily recognize that the methods of the invention can be used to modify any eukaryotic cell. Applicants argue that there is no requirement that the methods of the invention be restricted to ES cells, or to mouse ES cells. Applicants point to scientific literature which reveals that much research has been performed in which endogenous genes and chromosomal loci are variously modified in a wide

assortment of eukaryotic cells. See p. 7. Applicants further argue that ES cell technology is not limited to the mouse system and present various references to support this. See p. 8, 2nd ¶. Furthermore, Applicants argue that the methods of the invention only require that the vectors described herein be capable of homologous recombination with the target cell, and that cells other than ES cells can be used for the methods of the invention. Thus, Applicants argue that the Examiner has not provided persuasive reason(s) as to why the specification does not realistically enable one skilled in the art to practice the claimed invention using any eukaryotic cell, including any ES cell. Applicants state that even if the use of ES cell technology has not been perfected in some species, the claimed methods could certainly be used on any ES cell or any eukaryotic cell. See p. 8, 3rd ¶.

Applicants' arguments have been carefully considered but are not found to be persuasive. The specification teaches the generation of mouse ES cells having a deletion of the OCR10 gene (Example 1), however, the specification does not provide teachings to that shows that the claimed transgenic mice would be able to correctly produce chimeric or human antibodies as claimed, and as the specification and art support, such production would be considered unpredictable. In particular, because the enabled use of the genetically modified eukaryotic cells is to produce transgenic non-human organisms. See p. 8, lines 8-11, the prior rejection of record is found to be proper and is maintained for reasons of record. With regard to the availability of ES cells from other species, it is noted that Applicants state that these are

pluripotent cells. That is, that ES cells from other species fail to demonstrate that the ES cells to give rise to germline tissue or the whole animal, a demonstration which is an art-recognized property of ES cells. See also prior Office action, Moreadith *et al.* Although particular transgenic animals have been produced, the state of the art of producing ES cells from any particular species is found to be unpredictable. Applicants argue that the reference cited by the Examiner previously is relatively old, and does not reflect the state of the art of the time that the current invention was filed. The Examiner provides Pera *et al.* [**Journal of Cell Science** 113: 5-10 (2000)] who present the generic criteria for pluripotent ES or EG cells [see p. 6, 2nd column] and state that, "Thus far, only mouse EG or ES cells meet these generic criteria. Primate ES cells meet the first three of the four criteria, but not the last. Numerous other candidate mammalian ES cells have been described over the years in domestic and laboratory species, but only in the mouse have all criteria been met rigorously." [See p. 6, 2nd column, last paragraph]. Thus, it is maintained that because the only taught use for the genetically modified eukaryotic cells is to produce transgenic animals expressing a particular transgene, ES cells are found to be critical to the invention. Finally, in response to Applicants' argument that homologous recombination occurs in cells other than ES cells, it is noted that the only enabled use of the genetically modified eukaryotic cells is to produce transgenic animals. Thus, although eukaryotic cells do homologously recombine, the specification provides no enabled use for those cells other than to

produce transgenic animals. Accordingly it is maintained that only mouse ES cells would be available to use in the claimed methods to produce transgenic mice, as specifically taught by the specification.

Accordingly, in view of the quantity of experimentation necessary for the use of ES cells from species other than mouse, the lack of direction or guidance, as well as the absence of working examples, provided by the specification for methods of genetically modifying ES cells from species other than mouse, as well as the unpredictable and undeveloped state of the art of ES cells, and the breadth of the claims encompassing any species of ES cells, it would have required undue experimentation for one skilled in the art to make and/or use the claimed genetically modified ES cells, and methods of using the same.

### *Claim Rejections - 35 USC § 112*

The prior rejection of claims 51-53, 65-67 and 75 is withdrawn in view of Applicants' amendment to the claims to recite the term isolated.

The prior rejection of claims 61, 62, 72, 77, 78 are rendered moot in view of Applicants' cancellation of the claims.

### *Claim Rejections - 35 USC § 102*

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 51-55, 57-60, 63, 65-69, 71, 75 and 76 are rejected under 35 U.S.C. 102(b) as being anticipated by Kuncherlapati *et al.* (cited previously). This rejection is maintained for reasons of record.

Kuncherlapati *et al.* teach a method of using yeast artificial chromosomes [YACS] to produce mouse ES cells which have nonfunctional endogenous immunoglobulin genes, and have been introduced with xenogeneic, e.g., human heavy and light chain immunoglobulin genes [see p. 10, lines 27-37 and p. 11, lines 1-16]. Kuncherlapati *et al.* teach that the host immunoglobulin loci (both heavy chain alleles and both light chain alleles (kappa and lambda)) would be rendered non-functional by homologous recombination by the introduction of homologous DNA via a construct that can disrupt or delete the target locus in embryonic stem cells. Further, Kuncherlapati *et al.* teach that in order to functionally inactivate each of the loci, there may be multiple transformations [see pp. 14-15, bridging paragraph]. Kuncherlapati *et al.* teach that in order to verify that homologous double crossover has occurred, negative selection (such as the Herpes simplex virus thymidine kinase gene) may be employed, furthermore to determine if homologous integration has occurred, DNA analysis by Southern blot hybridization can be used to establish the location of integration. Additionally, PCR may be used, wherein the PCR primers are complementary to a sequence within the targeting construct and

complementary to a sequence and at the target locus to show that homologous recombination as occurred [see p. 17].

Applicants argue that Kuncherlapati do not anticipate the claimed invention because they do not teach or suggest 1) homologous recombination of large DNA vectors equivalent to a LTVEC (*e.g.*, having homology arms that total greater than 20 kb), 2) targeted integration, 3) modifying an endogenous gene locus with site specific recombination sites or 4) use of a qualitative assay to detect a modified cell. Applicants argue that Kuncherlapati teach using YACS, which are introduced by random mutation and point to p. 12, lines 25-29 for support of this. Applicants further argue that they do not teach the use of quantitative assays, including quantitative PCR, to detect whether or not homologous recombination occurs. Applicants aruge that the Examiner stated that Kuncherlapati teaches DNA analysis by Southern blot hybridization, or (junctional) PCR, and that neither of these assays are the quantitative assays required by the claims. Applicants argue that these assays detect correct targeting by qualitatively probing across homology arms of the targeting vectors, and that the quantitative MOA assays of the instant claims does not require probing across the homology arms of the vectors. Further, Applicants argue that the instant claims require the creation of flanking site-specific recombination sites, which is not a feature taught by Kuncherlapati. See pp. 9-10 of the Response.

Applicants' arguments have been carefully considered but are not found to be persuasive. With regard to Applicants' arguments that Kuncherlapati do not disclose homologous recombination of large vectors equivalent to a LTVEC, and specifically that the homology arms, as taught by Kuncherlapati are not greater than 20 kb, is not persuasive because there is no limitation required by the claim that the arms of homology be greater than 20 kb. The specification defines a LTVEC as a, "Large targeting vectors for eukaryotic cells that are derived from fragments of cloned genomic DNA larger than those typically used by other approaches intended to perform homologous targeting events in eukaryotic cells." Thus, the vectors, as taught by Kuncherlapati anticipate the claimed invention because they fulfill the definition of LTVEC. With regard to Applicants arguments that Kuncherlapati do not teach targeted integration or modifying an endogenous gene locus with site-specific recombination sites, the Examiner points to pp. 14-15 of Kuncherlapati who specifically state, "To render the host immunoglobulin loci non-functional, homologous recombination may be employed, where DNA is introduced at the endogenous host immunoglobulin heavy chain and light chain loci which inhibits the production of endogenous immunoglobulin." Thus, Kuncherlapati teach targeted integration in an endogenous gene locus using site-specific recombination sites. It is noted that both the instantly claimed method and the methods taught by Kuncherlapati are in general, considered random, because although they both are to targeted integration, the integration itself is considered random with regard to if

the insertion event occurs or not. With regard to Applicants' arguments that Southern blotting, as taught by Kuncherlapati is not considered quantitative, it is noted that the specification teaches that one quantitative assays for modification of allele (MOA) specifically contemplated by the specification is quantitative hybridization to an immobilized probe (Southern), see p. 30, lines 32-34. Thus, the instant specification even contemplates using Southern blotting as a quantitative assay in the claimed methods. It is finally noted that the term quantitative encompasses providing a positive or negative result.

Accordingly, Kuncherlapati *et al.* anticipate the claimed invention.

### *Claim Rejections - 35 USC § 103*

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor

and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 51-58, 60, 63, 65-71 and 75-76 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kuncherlapati *et al.* when taken with Yang *et al.* This rejection if maintained for reasons of record.

Kuncherlapati *et al.* is described in detail above. Kuncherlapati *et al.* differ from the claimed invention in that they do not teach the use of bacterial homologous recombination to replace an endogenous immunoglobulin variable region gene locus with a homolgous or othologous human gene locus. However, prior to the time of the claimed invention, Yang *et al.* teach using bacterial artificial chromosomes [BACs] to generate transgenic mice expressing a lacZ transgene [see *Abstract* and page 863]. Particularly, Yang *et al.* teach using a BAC for targeted recombination [see Figure 1, p. 860]. Accordingly, in view of the combined teachings of Yang *et al.* and Kuncherlapati *et al.*, it would have been obvious to modify the method of using yeast artificial chromosomes [YACS] to produce mouse ES cells which have nonfunctional endogenous immunoglobulin genes, and have been introduced with xenogeneic, e.g., human heavy and light chain immunoglobulin genes of Kuncherlapati *et al.* using BACs as described by Yang *et al.*, with a reasonable expectation of success. One of skill in the art would have been sufficiently motivated

to make such a modification, as asserted by Yang *et al.* who state that using BAC systems to target homologous recombination overcomes various limitations of using YACs, such as, BAC libraries are easier to construct due to higher cloning efficiency, BACs have high stability and minimal chimerism, and BAC DNA is easy to isolate [see p. 859, 2nd column, 1st paragraph and p. 864, 1st paragraph].

Applicants argue that, as stated in the response for 102, Kuncherlapati do not teach or suggest the claimed invention. The response these arguments have been addressed above. Applicants argue that Yang does not teach or disclose 1) targeted integration, 2) the use of site-specific recombination sites or 3) the use of a quantitative assay to detect a modified cell. It is noted that Yang is referred to in this rejection because they teach the use of bacterial homologous recombination in order to replace an endogenous locus. Applicants argue that the examiner has not established a *prima facie* case of obviousness because neither of the references teach the claimed invention, particularly, 1) targeted integration, 2) the use of site-specific recombination sites or 3) the use of a quantitative assay to detect a modified cell. It is maintained that Kuncherlapati teach the three points argued by Applicants above (as responded to above) and the combination of Kuncherlapati and Yang have sufficient motivation to render the claimed invention obvious.

Thus, the claimed invention as a whole was clearly *prima facie* obvious at the time the claimed invention was made especially in the absence of sufficient, clear and convincing evidence to the contrary.

Claim 51-55, 57-58, 60, 63-69, 71, 75-78 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kuncherlapati *et al.* when taken with Lie *et al.* This rejection is maintained for reasons of record.

Kuncherlapati *et al.* is described in detail above. Kuncherlapati differ from the claimed invention in that they do not teach or suggest using quantitative PCR comprising TaqMan® technology or quantitative PCR using molecular beacons. However, prior to the time of the claimed invention, Lie *et al.* teach advances in PCR quantitation, using TaqMan [see p. 43, 1st column, last paragraph]. Lie *et al.* teach that TaqMan can be used to quantify the number of copies of a DNA template in a genomic DNA sample [see p. 46-47]. Accordingly, it would have been obvious for one of skill in the art to modify the method of using BACs to produce mouse ES cells which have nonfunctional endogenous immunoglobulin genes, and have been introduced with xenogeneic, e.g., human heavy and light chain immunoglobulin genes as taught by Kuncherlapati *et al.* and Yang *et al.* by using a quantitative assay using TaqMan, as taught by Lie *et al.*, with a reasonable expectation of success. One of skill in the art would have been motivated to make such a modification, as there was an art-recognized need to improve quantitative PCR methods to evaluate factors such as gene copy numbers, mRNA expression, the efficiency of gene delivery systems, as asserted by Lie *et al.*, p. 43, 2nd paragraph.

Applicants argue that, as stated in the response for 102, Kuncherlapati do not teach or suggest the claimed invention. The response these arguments have been addressed above. Applicants argue that Lie does not teach or disclose 1) targeted integration, 2) the use of site-specific recombination sites or 3) the use of a quantitative assay to detect a modified cell. It is noted that Lie is referred to in this rejection because they teach advances in quantitative PCR technology, and in particular Taqman technology. Applicants argue that the examiner has not established a *prima facie* case of obviousness because neither of the references teach the claimed invention, particularly, 1) targeted integration, 2) the use of site-specific recombination sites or 3) the use of a quantitative assay to detect a modified cell. It is maintained that Kuncherlapati teach the three points argued by Applicants above (as responded to above) and the combination of Kuncherlapati and Lie have sufficient motivation to render the claimed invention obvious.

Thus the claimed invention as a whole was clearly *prima facie* obvious at the time the claimed invention was made especially in the absence of sufficient, clear and convincing evidence to the contrary.

***Conclusion***

No claim is allowed.

**THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Thaian N. Ton whose telephone number is (571) 272-0736. The Examiner can normally be reached on Monday through Friday from 8:00 to 5:00 (Eastern Standard Time), with alternating Fridays off. Should the Examiner be unavailable, inquiries should be directed to Ram Shukla, SPE of Art Unit 1632, at (571) 272-0735. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the Official Fax at (571) 273-8300. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989).

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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